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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,234	09/25/2006	Stephen Robert Wedge	056291-5304	1864

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EXAMINER	
WELTER, RACHAEL E	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,234	WEDGE, STEPHEN ROBERT	
	Examiner	Art Unit	
	RACHAEL E. WELTER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,12-21,23 and 24* is/are pending in the application.

4a) Of the above claim(s) *12-18 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,19-21,and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/09, 9/30/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 10, 12-21, and 23-24 are pending. Claims 10, 19-21 and 23 are drawn to the elected invention. Claims 12-18 and 24 are withdrawn. Claims 1-9, 11, and 22 are cancelled.

Acknowledgements

Receipt of the amendment and remarks/arguments filed on 9/30/09 is acknowledged.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on November 13, 2009 and September 30, 2009 are in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statements were considered by the examiner. A signed copy of forms 1449 are enclosed herewith.

Withdrawn Rejections

The rejection of claims 10, 19-23 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 7 of copending application 10/563,439, in view of Ple (US Patent 7,462,623) is withdrawn in light of the copending application's abandonment.

The rejection of claims 10, 19, and 21-23 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of copending application 11/663,912 in view of Ple (US Patent 7,462,623), and further in view of Zeldis (US Patent 7,468,363) is withdrawn in light of the copending application's abandonment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 10, 19, 21, and 23 rejected under 103(a) as being unpatentable over Stokes et al. (WO 00/47212; equivalent to US Patent 7,074,800), as evidenced Li et al. (US Patent 5,977,163) is maintained.

Stokes et al teach compositions comprising certain angiogenesis inhibitors, including AZD2171, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier (see abstract and reference claim 12). Stokes et al teach antiangiogenic compounds, including AZD2171 (see reference claim 12), or pharmaceutically acceptable salts, for use in the manufacture of medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being (see also col. 62, lines 1-35). Stokes et al teach that in the field of oncology, it is normal practice to use a combination of different forms

of treatment to treat each patient with cancer (col. 62, lines 42-45). Stokes et al teach that conjoint treatment with surgery, radiotherapy or chemotherapy may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment (col. 62, line 36 to col. 63, line 32, especially, col. 62, lines 40-42). In particular, Stokes et al disclose antiproliferative/antineoplastic agents such as a taxoid like taxol and taxotere (also known as docetaxel) to be suitable for use in combination with said antiangiogenic compounds (col. 63, lines 11-32, especially line 23).

The above discussion of Stokes et al is incorporated by reference. However, Stokes et al do not expressly teach that docetaxol is the same as taxotere.

Li et al is added as an evidentiary reference only for its teaching that taxotere as taught by Stokes et al is also known as docetaxel (abstract).

It would have been obvious to a person of skill in the art at the time the invention was made to combine any compound species of formula 1, including applicant's claimed compound, with any suitable conventionally known antiproliferative/ antineoplastic drug (e.g. taxotere), and a pharmaceutically acceptable excipient or carrier as taught by Stokes et al for additive therapeutic effects (col. 63, lines 11-27; see also reference claims 12 and 25). One would have been motivated to do so because Stokes et al suggest that compounds of formula I, including applicant's claimed compound, may be combined with any known suitable antiproliferative/antineoplastic agent (e.g. taxotere; col. 63, line 23). The motivation for combining the components

flows from their individually known common utility (see *In re Kerkhoven, 205 USPQ 1069 (CCPPA 1980)*.

Regarding claims 10, 19, and 21, Stokes et al teach AZD2171 free base and pharmaceutically salts thereof (reference claim 12).

Regarding claim 23, Stokes et al teach taxotere, which is also known as docetaxel as evidenced by the teaching of Li et al (abstract).

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

The rejection of claim 20 rejected under 103(a) as being unpatentable over Stokes et al. (WO 00/47212; equivalent to US Patent 7,074,800), as evidenced Li et al. (US Patent 5,977,163) in view of Penkler et al (6,255,502) is maintained.

The above discussion of Stokes et al is incorporated by reference. However, Stokes et al do not teach maleate salt.

Penkler et al teach compositions comprising pharmaceutical actives capable of existing in both free base and acid addition salt form, wherein the acids used include hydrochloride, and maleate salts (col. 2, lines 38-42).

It would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references to select any suitable acid addition salt of AZD2171, including applicant's maleate salt, for use in a pharmaceutical composition. One would have been motivated to do so because Penkler et al suggest

acid addition salts forms (e.g. maleate and hydrochloride) can be prepared for compounds that are capable of existing in both free base and acid addition salt form (col. 2, lines 38-42) and Stokes et al teach that compounds (e.g. AZD2171) that are capable of existing in both the free base and acid addition salt form (e.g. hydrochloride salt; col. 46, line 55 and reference claim 12). As such, one would reasonably expect to successfully prepare a maleate salt form of AZD2171 for use in a composition as taught by Stokes et al since both maleate and hydrochloride salts are acid addition salts as evidenced by the teaching of Penkler et al (col. 2, lines 38-42).

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Response to Arguments

Applicant's arguments filed 9/30/09 and 1.132 Declaration filed 2/13/09 have been fully considered but they are unpersuasive and insufficient.

Applicant first argues that there is no disclosure or suggestion in Stokes of a specific combination of AZD2171 and taxane. Applicant submits that no preference is expressed for any particular angiogenesis inhibitor to use in such combination and there is nothing in the disclosure to specifically select docetaxel or paclitaxel out of the enormous listing of possibilities. Applicant argues that when considering a prior art reference, it is required to consider the reference as a whole and not just select out isolated disclosures for combination, which applicant argues that the examiner could

only have done by impermissible use of hindsight. Applicant disagrees with the examiner's citing of Kerkhoven and KSR and notes that Li nor Penkler fail to address the deficiencies of Stokes.

The examiner disagrees with applicant and maintains the position that it is within the skill of an artisan to try the instant combination of AZD2171 and a taxane given the teachings in the prior art. The examiner notes that it would have been obvious to an artisan of ordinary skill at the time the invention was made to select from the finite possibilities and arrive at the instantly claimed composition. In KSR v. Telefex, 82 USPQ2d 1385, 1397 (U.S. 2007), the Supreme Court has held that when there is market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person has good reason to pursue known options within his or her technical grasp. Under these conditions, "obviousness to try" such options is permissible. Therefore, one would have been motivated to try the combination of AZD2171 and a taxane because Stokes suggests it within a finite number of identified possibilities. Even though Stokes may describe more than one angiogenesis inhibitor and list many agents that can be combined with such inhibitors, there is not an infinite list of combinations and thus it is not beyond the means of an ordinary skilled artisan. According to MPEP 2145, "...obvious to try [is] to explore a new technology or general approach that [seems] to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988).*

Additionally, the examiner contends that one would be motivated to combine a taxane and the instant inhibitor because Stokes suggests that they both can be used to combat cancer. Since Stokes suggests that it is normal practice to use a combination of different forms of treatment to treat each patient with cancer, an artisan of ordinary skill would reasonably expect that the combined administration of the instant inhibitor and the taxane would result in a complementary or possibly synergistic effect. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)* (see MPEP 2144.06). Even though applicant argues that Kerkhoven is drawn to a mechanical application, it is the position of the examiner that this case law can be applied within the pharmaceutical arts. Applicant is merely arguing. Burden is on applicant to prove that their composition has a greater than additive effect in the art than would normally be expected.

Applicant further submits the Wedge Declaration demonstrating unexpected significantly greater efficacy with the claimed combination as opposed to either component alone. Applicant further supports this evidence with references, Wu and Furutani Abstracts.

In response to applicant's Declaration and the cited references, the examiner directs applicant's attention to MPEP 716.02 (a), which states that "...a greater than additive effect is not necessarily sufficient to overcome a prima facie case of

obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage." *Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991).* In this case, the examiner notes that such results would be expected rather than unexpected because it is routine in the oncology art to combine two or more compounds for use in the treatment of cancer to produce an additive effect and Stokes suggests that compounds of formula I, including AZD2171, may be combined with another antiprolliferative/antineoplastic drug, such as docetaxel to treat cancer. The examiner notes that applicant has failed to show that the instant combination results in a greater than additive effect than what would be expected with a significant and practical advantage.

Additionally, the examiner maintains the position that the submitted cited references and Declaration are not commensurate in scope with the instant claims. According to MPEP 716.02, whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980).* The examiner notes that applicant only showed results and provided evidence in the cited references with specific dosages of AZD2171 and docetaxel formulations (i.e., 3 mg/kg of AZD2171 and

10 mg/kg of docetaxel). Although applicant cites *In re Chupp*, the examiner contends that applicant claims no amount of the instant inhibitor and taxane. Thus, applicant's data is inadequate in providing unexpected results because applicant has only provided specific amounts of the instant compound and taxane and not compared it to results with varied amounts of these components. Even though applicant argues that adding dosage ranges to the instant claims would require applicant to conduct human clinical trials in order to obtain a claim scope that would encompass human subjects, it is not clear from the results whether using any amount of AZD2171and taxane would result in greater inhibition of tumor growth. Furthermore, the examiner notes that applicant's claims are not directed to a method of treatment or route of administration. The examiner notes that the Declaration and the cited references describe the instant inhibitor being administered orally and the taxane being administered via injection. However, the instant claims have no suggested route of administration. Finally, the examiner contends that the response to arguments presented herein is not questioning enablement or utility. The examiner notes that it is not disputed that the current pending claims are enabled and possess utility.

Thus, the alleged unexpected results are insufficient because they are not commensurate in scope with the instant claims and are expected rather than unexpected. The rejection is maintained for the reasons stated above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10, 19, 21, and 23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 9 of copending application 11/994,824, in view of Ple (US Patent 7,462,623), and further in view of Zeldis (US Patent 7,468,363).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims.

It is noted that the reference claims are directed to compositions comprising AZD2171 in combination with gemcitabine and a pharmaceutically acceptable carrier or excipient. Unlike the instant claims, the reference claims are not directed to combinations comprising taxane compounds (i.e. taxotere).

Ple teaches anti-tumor quinazoline derivative compounds which are useful in methods of treating solid tumors in humans or animals (col. 1, lines 4-13). Ple states that said compounds may be applied as a sole therapy or may involve, in addition to the quinazoline derivative compound, conventional surgery or radiotherapy or chemotherapy (col. 3, lines 53-56; col. 43, lines 22-58). Ple teach that the chemotherapy may include one or more categories of anti-tumor agents, including antiproliferative/antineoplastic drugs and combinations thereof (e.g. taxoids like taxol and taxotere; col. 43, lines 31-44); ..., and inhibitors of growth factor function (e.g. gefitnib, ZD1839).

Zeldis teach small molecule anti-cancer drugs, including docetaxel (col. 15, line 2) and gemcitabine (col. 15, line 12-13).

It would have been obvious to a person of skill in the art at the time the invention was made to manipulate the reference combination of AZD2171 and gemcitabine by substituting the gemcitabine with any suitable conventionally known chemotherapy (e.g. taxotere) as taught by Ple (col. 43, line 44) to arrive at the instant claimed invention (AZD2171 in combination with taxotere) for use in treating solid tumors in humans. One would have been motivated to do so because Zeldis suggest that docetaxel and gemcitabine are equivalent small molecule anti-cancer drugs. Further, Ple suggest that quinoazoline derivative compounds with anti-tumor activity can be combined with one or more chemotherapy (e.g. taxotere) to treat solid tumors in human and the reference claims are also directed to a combination comprising a quinazoline derivative compound (e.g. AZD2171) and a chemotherapy agent (e.g.

gemcitaine). Hence, one would reasonably expect to successfully substitute the gemcitaine component of the reference claims with taxotere as taught by Ple and combine it with AZD2171 since both the reference claims and Ple are directed to combinations comprising an anti-tumor quinazoline compound and another chemotherapy drug. Besides, it is routine in the oncology art to use combination of chemotherapy comprising different drugs for treating cancers in order to reduce the potential for the development of cancer resistant cells to the chemotherapy.

For the reasons stated above, claims 10 and 19-23 are deemed to be obvious variants of the limitations of the claimed subject matter of the above cited copending applications in view of Ple, and further in view of Zeldis.

These rejections are provisional obviousness-type double patenting rejections because the conflicting claims of the copending applications have not in fact been patented.

Response to Arguments

Applicant's request to hold the nonstatutory obviousness-type double patenting rejections in abeyance pending a finding of allowable subject matter is acknowledged. Since applicant has not substantially traversed the rejection, the rejection is maintained for the reasons of record.

Conclusion

Claims 10, 19-21, and 23 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RACHAEL E. WELTER whose telephone number is (571) 270-5237. The examiner can normally be reached 7:30-5:00 Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

REW

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611
March 27, 2010